Does dexamethasone suppress the ACTH response in preterm babies?

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SUMMARY Tests of adrenal stimulation with adrenocorticotrophic hormone (ACTH) were performed before and after commencing dexamethasone treatment in 12 infants. All except one of the tests performed showed the expected twofold rise in serum cortisol, suggesting that in this group of premature babies dexamethasone did not suppress the adrenal response.

Dexamethasone treatment has been shown to be effective in reducing the respiratory support required by infants who are still ventilator dependent at 3 weeks postnatal age.¹ The dose recommended as a result of such studies is high, treatment usually commencing with 0.5 mg/kg/day. Preterm babies are often subject to intercurrent stress from surgery or infection and in view of the increasing use of dexamethasone treatment for bronchopulmonary dysplasia it seemed important to document whether such treatment resulted in adrenal suppression. A short ACTH test has been shown to be reliable in predicting the stress response to surgery in adult patients.² The preterm infant is normally capable of responding to ACTH at a dose of 36 µg/kg with a two to threefold rise in serum cortisol concentration at one hour,³ and so this method was chosen to evaluate adrenal response in a group of dexamethasone treated babies.

Subjects and methods

A group of 12 preterm infants who had been treated in the Cambridge neonatal intensive care unit during 1986–7 were studied. They had a mean gestational age of 26 weeks (range 23–29 weeks) and mean birth weight of 968 g (range 616–1735 g). The ventilatory support required before the administration of dexamethasone was positive pressure ventilation in 10 and an inspired oxygen of >30% in two. Mean postnatal age at the start of treatment was 22 days (range from 9–45 days). Courses lasted a mean of 13 days (range 3–28 days) with a dose regime similar to that used by Avery *et al.*: commencing with 0.5 mg/kg/day given intravenously in two divided doses

for three days, then with a 10% dose reduction 72 hourly until the end of the course.¹ Ventilatory support was reduced after treatment in seven babies. There were four positive blood cultures after commencement of treatment, and one gastrointestinal perforation. Seven of the infants did not survive in the long term, one remaining ventilated in 80% oxygen at the age of 7 months, and one has cerebral palsy at 18 months. Only three of the babies had a normal outcome.

ACTH (Synacthen) was given in a dose of 36 µg/kg intramuscularly and venous or arterial blood samples drawn for cortisol estimation before and one hour after the dose.³ Tests were performed at midnight before, during, and after treatment. Two of the babies had samples collected shortly before the end of a course, and 10 had samples collected between five and 28 days after treatment had ceased. Serum cortisol was determined on duplicate 25 µl samples by radioimmunoassay (Gamma-BCT cortisol kit, RIA (UK) Ltd). Cross sensitivity of antibody was: prednisolone 28%, corticosterone 8%, prednisone 2.1%, and dexamethasone <0.05%. For comparison of groups of cortisol values the Mann-Whitney rank sum test was used. The study was approved by the local ethical committee.

Results

Both before and after treatment all except one of the ACTH tests showed the expected twofold rise in cortisol concentration (figure). Median and interquartile range of cortisol before treatment was 98 nmol/l (83–131) rising to 544 nmol/l (77–229) and after treatment 105 nmol/l (76–229) rising to 603 nmol/l (496–717). There was thus no evidence of blunting and there was a significant rise in both groups ($p=0.01$, Mann-Whitney). No relation was observed between either serum cortisol concentration or the degree of the response with postnatal age or duration of dexamethasone treatment.

Discussion

In this group of premature babies dexamethasone

Figure Serum cortisol concentration before and after ACTH in babies treated with dexamethasone and before and after steroid treatment.

treatment did not suppress or blunt the cortisol response to ACTH up to 28 days after cessation of treatment. Even in the subgroup of five infants tested between two days before and seven days after the end of treatment no suppression was seen. This was a surprising finding as we used the relatively high dose of dexamethasone recommended for bronchopulmonary dysplasia. Furthermore it was interesting that basal cortisol concentrations were the same before and after treatment, although these data do not preclude a fall in plasma cortisol during treatment.

The daily dose of dexamethasone used here and in similar studies would be equivalent to a prednisolone dose of 3 mg/kg/day.¹ Adult patients treated with 25 mg twice daily (less than 1 mg/kg) exhibited a blunted cortisol response.⁴ The cortisol response in infants has been shown to be preserved after maternal betamethasone treatment,⁵ although the cord blood cortisol concentration was suppressed. Furthermore, in the study of Thomas *et al* five ill

infants still mounted an adequate response to ACTH despite absent basal cortisol concentrations.³ One possible explanation for these and our own findings might be that the ACTH stimulus was relatively larger than that normally applied in adults. The dose of ACTH required to produce a cortisol response similar to that of hypoglycaemia in adults is only 0.2 µg/kg intravenously, suggesting that the usual dose of 250 µg (5 µg/kg) for an adult ACTH test is far in excess of that needed to raise a response. Probably in all the ACTH regimes commonly used in adults and children the dose of ACTH is larger than the amount required to stimulate the adrenal, so that the lack of dexamethasone suppression observed in this study is unlikely to relate to the dose of ACTH chosen. At the time that the babies in this study were investigated the hyperaemic fetal zone of the adrenal gland would not have involuted to the half size that is documented at one month,⁶ and it may be that this was the reason for the preserved response.

The objective of this study was to examine the cortisol response after dexamethasone treatment; while we cannot comment on the response during treatment, these preliminary data suggest that after a complete course of dexamethasone treatment steroid replacement therapy for intercurrent infection or surgery may not always be necessary.

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